EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Afstyla 200IU Powder & Solvent for Solution For injection
Afstyla 500IU Powder & Solvent for Solution For injection
Afstyla 1000 IU Powder & Solvent for Solution For injection

Date: March 2024

Unit: Technical Assessment Unit

Assessment report

Afstyla

Administrative information:

Trade name of the medicinal product:	Afstyla
INN (or common name) of the active substance(s):	Recombinant, single chain coagulation factor VIII (rVIII-single chain)
Manufacturer of the finished product	CSL Behring GmbH Görzhäuser Hof D-35041 Marburg - Germany
Marketing Authorization holder	CSL Behring GmbH Emil-von-Behring-Straβe 76, D-35041 Marburg-Germany
Applied Indication(s):	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor XIII deficiency).
Pharmaceutical form(s) and strength(s):	• Powder and solvent for solution for injection • Strengths: 250 IU, 500 IU & 1000 IU
Route of administration	All concentrations are intended for Intravenous use (I.V)
Approved Pack	**AFSTYLA 250 IU**: Carton box containing clear, neutral borosilicate glass (Type 1) vial closed with bromo butyl rubber stopper. The stoppers are secured by combination caps consisting of a green striped aluminum crimp cap with a concentric hole and an integrated polypropylene orange plastic disc and reconstituted with 2.5 ml water for injection, 1 filter transfer device 20/20 (mix2vial),1 disposable 5ml syringe,1venipunctre set,2 alcohol swabs,1 non -sterile plaster with insert leaflet. **Diluent:** Glass (type 1) vial of 2.5 ml in 6 ml closed with grey, Bromo butyl rubber G1525 and Combi cap, aluminum/polypropylene, blue/lime,5000212 **AFSTYLA 500 IU:** Carton box containing clear, neutral borosilicate glass (Type 1) vial closed with Bromo butyl rubber stopper. The stoppers are secured by combination caps consisting of a green striped aluminum crimp cap with a concentric hole and an integrated polypropylene blue plastic disc and reconstituted with 2.5 ml water for

	injection, 1 filter transfer device 20/20 (mix2vial),1 disposable 5ml syringe,1venipunctre set,2 alcohol swabs,1 non -sterile plaster with insert leaflet. **Diluent:** Glass (type 1) vial of 2.5 ml in 6 ml closed with grey, Bromo butyl rubber G1525 and Combi cap, aluminum/polypropylene, blue/lime,5000212 **AFSTYLA 1000 IU:** Carton box containing clear, neutral borosilicate glass (Type 1) vial closed with bromo butyl rubber stopper. The stoppers are secured by combination caps consisting of a green striped aluminum crimp cap with a concentric hole and an integrated polypropylene green plastic disc and reconstituted with 2.5 ml water for injection, 1 filter transfer device 20/20 (mix2vial),1 disposable 5ml syringe,1venipunctre set,2 alcohol swabs,1 non -sterile plaster with insert leaflet. **Diluent**: Glass (type 1) vial of 2.5 ml in 6 ml closed with grey, Bromo butyl rubber G1525 and Combi cap, aluminum/polypropylene, blue/lime,5000212

List of abbreviations

AS	Active substance
CTD	Common technical document
EMA	European Medicines Agency
I.V	Intravenous
IU	International unit
sWFI	Sterile water for injection
WFI	Water for injection

Dossier initial submission and evaluation process.

- The product was submitted for registration via reliance model level 1
- The applicant applied for scientific advice unit on 1.6.2022
- The dossier was initially received by the registration administration units on 28.2.2023 after providing all the required documents (EMA detailed unredacted assessment report along with Full CTD for the product).

1. **General introduction about the product including brief description of the AI, its mode of action and indications**.

- The finished product is presented as a sterile, preservative-free, lyophilized powder and solvent (water for injections (WFI)) for solution for i.v. administration containing recombinant, single chain coagulation factor VIII (rVIII-SingleChain) as active substance.
- The product is available in the Egyptian market in three concentrations 250 IU, 500 IU and 1000 IU.
- The lyophilized finished product is reconstituted with sterile water for injections. For the 250 IU, 500 IU and 1000 IU strengths 2.5 ml of sWFI is used.
- Afstyla is indicated for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
- The active substance (AS) in Afstyla is "recombinant, single chain coagulation factor VIII", which is expressed and secreted by CHO cells.
- The active substance is a single-chain recombinant Factor VIII (rVIII-SingleChain) construct where most of the B-domain and 4 amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length FVIII, including the furin-cleavage site). The newly formed linkage of the heavy and light chain of FVIII introduces a new N-glycosylation site. It has 1444 amino acids in a single chain glycopeptide with a molecular weight of approximately 170 kDa.
- After activation by thrombin and removal of the (residual) B- and a3-domain, the activated rFVIII (rFVIIIa) molecule formed has an amino acid sequence identical to FVIIIa formed from endogenous, full length, FVIII. The three-dimensional structure of rVIII-SingleChain is stabilized by eight disulphide bridges. The presence of three "free thiols" has been confirmed. Regarding glycosylation, rVIII-SingleChain contains six N-glycosylation sites, but was found to have limited O-glycosylation. rVIII-SingleChain also exhibits nearly complete sulphation of its tyrosine residues.

2. **Quality aspects:**

- **Manufacturer(s)**

- The active substance is manufactured at CSL Behring GmbH Emil-von-Behring-Straβe 76 D-35041 Marburg – GERMANY.
-The finished product is manufactured at CSL Behring GmbH Gorzhauser Hof D-35041 Marburg Germany.
- All the manufacturing sites are authorized according to the current GMP regulations.

- **Stability**

Drug substance:

-Approved Shelf Life: 3 years
- Approved storage conditions: Store at ≤ -65 °C

Drug product:

-Approved storage conditions for drug product: Store in a refrigerator (2 - 8 °C), Do not freeze.

-Keep vials in the outer carton in order to protect from light.

-Approved Shelf Life: 3 years.

3. Non-clinical and clinical aspects:

-Generally, No special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity studies, local tolerability and thrombogenicity assessments.

-Furthermore, the non-clinical program for Afstyla demonstrated equal hemostatic efficacy in a comparative study with marketed rFVIII concentrates in a relevant animal model of FVIII deficiency, mimicking the disease state of hemophilia A patients from a clinical point of view in terms of a major bleeding/trauma. Therefore, Afstyla is considered as an effective and safe drug to treat hemophilia A patients from the preclinical point of view.

-In conclusion the overall benefit/risk of Afstyla 250 IU, 500 IU ,1000 IU are favorable in the treatment and the prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

- **General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/afstyla-epar-public-assessment-report_en.pdf